PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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18. Aug. 2004
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	17.08.2004
Applicant's or agent's file reference E 7823/WM	**IMPORTANT NOTIFICATION**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 03/03540	04.04.2003	05.04.2002

Applicant
EURO-CELTIQUE S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Longo, E Tel. +49 89 2399-8141

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference E 7823/WM	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/03540	International filing date *(day/month/year)* 04.04.2003	Priority date *(day/month/year)* 05.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/16		
Applicant EURO-CELTIQUE S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.08.2003	17.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Felder, C Telephone No. +49 89 2399-7852

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03540

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-40 as originally filed

Claims, Numbers

1-32 filed with telefax on 28.07.2004

Drawings, Sheets

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 99 32119 A (EURO CELTIQUE SA ;KAIKO ROBERT F (US); COLUCCI ROBERT D (US)) 1 July 1999 (1999-07-01)
D2: WO 99 32120 A (EURO CELTIQUE SA ;PALERMO PHILIP (US)) 1 July 1999 (1999-07-01)
D3: WO 03 007802 A (EURO CELTIQUE SA ;WRIGHT CURTIS (US); BREDER CHRISTOPHER D (US); C) 30 January 2003 (2003-01-30)
D4: US-A-4 457 933 (GORDON MAXWELL ET AL) 3 July 1984 (1984-07-03)
D5: GB-A-1 390 772 (ENDO LAB) 16 April 1975 (1975-04-16)

The present invention discloses storage stable pharmaceutical dosage forms comprising oxycodone **and** naloxone characterized in that the active compounds are released from the preparation in a sustained, invariant and independent manner, and methods of preparations thereof. Particularly, the invention relates to storage stable pharmaceutical dosage forms which comprise oxycodone and naloxone in a (non-swellable) diffusion matrix comprising ethyl cellulose, wherein the matrix is determined with respect to its essential release characteristics by ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol and wherein the active compounds are released from the matrix in a sustained, invariant independent manner.

1. Novelty

Document D1 (citations see ISR) discloses a pharmaceutical dosage form which comprises an orally therapeutically effective amount of an opoid agonist (oxycodone), and an opoid antagonist (naloxone) in a **controlled release matrix**, wherein the matrix comprises alkylcellulose (**preferred ethylcellulose**), at least one fatty alcohol (e.g. lauryl alcohol, cetyl alcohol etc.). Furthermore said dosage may comprises further ingredients such as diluents, fillers, binders, glidants (e.g.

dibutyl sebacate) etc. Said matrix comprises as already said preferred ethylcellulose and therefore should show at least similar characteristics as long as the production process is comparable. One of the (preferred) production process claimed in D1 is comparable to the claimed production processes (granulation; extrusion) in the present application.
Therefore, present claims 1-32 seem to be not novel over the prior art D1.

Document D2 (citations see ISR) discloses an pharmaceutical dosage form which comprises an orally therapeutically effective amount of an opoid analgesic (oxycodone) together with an opoid antagonist (naloxone) in a **controlled release matrix**, wherein the matrix comprises alkylcellulose (**preferred ethylcellulose**), at least one fatty alcohol (e.g. lauryl alcohol, cetyl alcohol etc.). Furthermore said dosage may comprises further ingredients such as diluents, fillers, binders, glidants (e.g. dibutyl sebacate) etc. Said matrix comprises as already said preferred ethylcellulose and therefore should show at least similar characteristics as long as the production process is comparable. One of the (preferred) production process claimed in D1 is comparable to the claimed production processes (granulation; extrusion) in the present application.
Therefore, present claims 1-32 seem to be not novel over the prior art D2.

2. Inventive step

A person skilled in the art with the problem to develop a sustained release matrix dosage form of a combination of oxycodone with naloxone would find especially the teaching document D1 and D2 very helpful since they are dealing with sustained release dosage forms of opoids (D1 and D2). Furthermore, document D4 and D5 (citations see ISR), both disclose an pharmaceutical dosage form which comprises an orally therapeutically effective amount of a strong opoid analgesic (oxycodone) together with an opoid antagonist (naloxone) in a controlled release matrix.
The person skilled in the art would combine the teaching D4 and/or D5 and the teaching from D1 and/or D2 for developing a sustained release dosage form according to the present application (storage stable pharmaceutical dosage forms which comprise oxycodone and naloxone in a (non-swellable) diffusion matrix wherein the matrix is determined with respect to its essential release

characteristics by ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol and wherein the active compounds are released from the matrix in a sustained, invariant independent manner). Therefore, the subject matter of present claims 1-32 seems to not involve an inventive step.

3. Industrial applicability

All claims 1-32 of the present application are industrial applicable.